DSM-5 ATTENUATED PSYCHOSIS SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE EVIDENCE

- Advances in diagnosis and treatment review-

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Key points

Question: What is the clinical validity of the DSM-5 Attenuated Psychosis Syndrome?

Finding: In this systematic review, the clinical validity of the DSM-5 Attenuated Psychosis Syndrome (DSM-5-APS) was tested against evidence-based validators (antecedent, concurrent and prognostic). DSM-5-APS has received substantial concurrent and prognostic validation, mostly from psychometric research in the field of the clinical high-risk state for psychosis, while precipitating and predisposing epidemiological factors, neurobiological research and treatments have been under-investigated.

Meaning: Although current evidence supports the potential clinical validity of the DSM-5-APS, more research should address the epidemiological profile of this diagnostic category, its predisposing and precipitating risk factors, neurobiological correlates and the effectiveness of treatments.

ABSTRACT

Importance: Since the release of DSM-5 Attenuated Psychosis Syndrome (DSM-5-APS) in 2013, several research studies have investigated its clinical validity. Although critical and narrative reviews have reviewed these progresses, no systematic review has comprehensively summarised the available evidence regarding the clinical validity of DSM-5-APS.

Objective: This systematic review and meta-analysis provide state-of-the-art evidence on the clinical validity of DSM-5-APS.

Data source*:* Web of Science database (Clarivate Analytics), Cochrane Central Register of Reviews, Ovid/PsychINFO, conference proceedings and trial registries.

Study selection*:* A multistep literature search up to 16 June 2019 was conducted following PRISMA and MOOSE guidelines and PROSPERO protocol, to include studies with original data investigating individuals with a DSM-5 APS or comparable designations.

Data extraction and synthesis: The results were summarised in tables and narratively synthesised against established evidence-based validators (antecedent, concurrent and prognostic). A quantitative meta-analysis was conducted to explore the risk of psychosis onset in individuals diagnosed with the DSM-5-APS.

Main outcome(s) and measure(s): For the systematic review: antecedent, concurrent and prognostic validators. For the meta-analysis: cumulative risk of psychosis onset at 6-month, 12-month, 24-month and 36-month.

Results: The systematic review included 56 articles, which reported on 124 validators: 15 antecedents, 55 concurrent and 54 prognostic. The epidemiological prevalence of the DSM-5-APS in the general non-help seeking young population is 0.3%; the prevalence

of the DSM-5-APS is variable in clinical samples. The inter-rater reliability for DSM-5-APS is comparable to that of other DSM-5 mental disorders and can be optimised by the use of specific psychometric instruments. The DSM-5-APS is associated with frequent depressive comorbid disorders, distress, suicidality and functional impairment. Across 23 prospective cohort studies, the meta-analytical risk of psychosis onset was 11% at 6 months, 15% at 12 months, 20% at 24 months and 23% at 36 months follow-up. Research into predisposing and precipitating epidemiological factors, neurobiological correlates and effective treatments for DSM-5-APS has been limited.

Conclusions and relevance: Over the recent years the DSM-5-APS has received substantial concurrent and prognostic validation, although mostly driven by research into the clinical high-risk state for psychosis. Precipitating and predisposing factors, neurobiological correlates and effective treatments are undetermined.

Key words: Psychosis, Attenuated Psychosis Syndrome; Attenuated Positive Symptom Syndrome; Schizophrenia; Prevention, Risk.

INTRODUCTION:

Six years ago, the DSM-5 introduced the Attenuated Psychosis Syndrome diagnosis[1] (DSM-5-APS) in the research appendix, Section III under "Conditions for further study", at page 783[1] (Table 1). However, the DSM-5-APS also appears in the main body of text (page 122), where it is featured with the official codable diagnosis (298.8) of "Other Specified Schizophrenia Spectrum Disorder and Other Psychotic Disorder"[1] (eTable 1). The rationale for introducing the DSM-5-APS was grounded on clinical research evidence from the Clinical High Risk state for Psychosis (CHR-P)[2], which has allowed preventive interventions to enter clinical practice[3]. Consequently, the diagnostic structure of the DSM-5-APS is based on a subset of CHR-P risk criteria (eIntroduction): Attenuated Positive Symptom Syndrome (APSS) risk criteria, as defined by the Structured Interview for Psychosis-Risk Syndromes (SIPS[4], from the second version, dated 8th June 1998[5,6], Table 1), and -to a lesser extent- Attenuated Psychotic Symptoms (APS) criteria, as defined by the Comprehensive Assessment of At-Risk Mental States (CAARMS[7]; Table 1).

Although the APSS, APS and DSM-5-APS all measure attenuated psychotic symptoms, there are substantial operationalisation differences across them (Table 1). The APSS and APS are measured through semi-structured interviews (SIPS and CAARMS respectively) that require specific psychometric training; conversely, the DSM-5-APS is unstructured and measured clinically -as for any other standard psychiatric diagnosis-. Consequently, the inter-rater agreement is very high within the SIPS[8] and CAARMS[9] but lower for the DSM-5-APS[10]. The psychosis onset is also defined psychometrically under the APSS and APS but clinically in the DSM-5-APS. Another key difference is that while the DSM-5-APS requires symptoms to be sufficiently distressing and disabling for the patient to warrant clinical attention (criterion D), this is not strictly required by the APSS or APS. The APS operationalisation substantially differs from the DSM-5-APS with

respect to frequency (criterion B) and onset (criterion C) of symptoms, requirements for differential diagnosis with other mental disorders (criterion E; the APS is transdiagnostic[11]), substance misuse (symptoms induced by alcohol and cannabis are included in the APS) and threshold of psychosis onset (criterion F; because of different operationalisations of BLIPS[12,13]).

Since the agreement between the DSM-5-APS and the APS in help-seeking individuals is only moderate[14], these two operationalisations are similar but not identical, and they cannot be interchangeably used, as much as the DSM-5 schizophrenia and the DSM-5 schizophreniform disorder share similarities but are distinctive diagnostic categories. The APSS and DSM-5-APS are more similar: all patients with APSS are also meeting DSM-5 APS criteria[15-18] and most -albeit not all- patients with DSM5-APS meet APSS criteria (43/44)[15]. However, disability and distress (criterion D) are not strictly part of the APSS (Table 1); to overcome this discrepancy the SIPS version 5.6 (dated 30 May 2014, p.44) has introduced an additional question to additionally rate criterion D of the DSM-5-APS (Table 1). Therefore, the SIPSv5.6.-DSM-5-APS can be used to psychometrically rate the DSM-5-APS.

This is the first systematic review, complemented by meta-analytical analyses, which comprehensively assesses the advancements in diagnosis and treatment specifically for DSM-5-APS or closely related operationalisations, as opposed to loosely focusing on CHR-P findings that are not directly comparable.

METHODS

The study (study protocol registered on PROSPERO (CRD42019139330) was conducted in accordance with Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA, eTable 2)[19] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE, eTable 3) guidelines[20].

Search strategy and selection criteria

A multi-step literature search was performed using the following keywords: ("Attenuated Psychosis Syndrome" OR "Attenuated Psychosis Symptoms Syndrome" OR "APS" OR "APSS"). First, Web of Science database (Clarivate Analytics) was searched, incorporating the Web of Science Core Collection, BIOSIS Citation Index, KCI-Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index, as well as Cochrane Central Register of Reviews, and Ovid/PsychINFO databases from inception, until 16 June 2019, in English. Second, data in relevant conference proceedings (Schizophrenia International Research Society, Early Intervention in Mental Health) and trial registries (https://clinicaltrials.gov) were searched. Third, the references of systematic reviews or meta-analyses that were retrieved were manually searched. Abstracts of articles identified that were not relevant were screened out. The remaining full-text articles were then assessed for inclusion eligibility against the inclusion and exclusion criteria.

Condition and individuals being studied

The inclusion criteria were: a) original studies, abstracts or conference proceedings with no restriction on the topic investigated; b) conducted in individuals meeting the DSM-5-APS, APSS or SIPSv.5.6-DSM-5-APS criteria (Table 1, the rationale is detailed in the introduction); c) studies published in English.

The exclusion criteria were: a) reviews, editorials or clinical cases; b) unpublished data; c) studies measuring attenuated psychotic symptoms outside the DSM-5-APS, APSS or SIPSv.5.6-DSM-5-APS criteria, such as those employing the Basel Screening Instrument for Psychosis (BSIP[21]) or Comprehensive Assessment of At-Risk Mental States (CAARMS[7]) (which are prognostically[14] but not diagnostically comparable to the DSM-5-

APS); d) studies that do not report specific information on the APSS group alone but reported composite results including other CHR-P subgroups (e.g. BLIPS and Genetic Risk and Deterioration Syndrome, GRD).

Outcome measures and data extraction

Data were independently extracted by two researchers (GSP, AC) and discrepancies were resolved consulting a third senior academic (PFP). The variables extracted included: validator (antecedent, concurrent, prognostic -see below), author and year of publication, study type (original or abstract), study design (cross-sectional, prospective, retrospective, intervention or naturalistic), type of diagnostic assessment (clinical or psychometric -including the SIPS version-; face to face, chart review or telephone), diagnostic operationalisation (DSM-5-APS, APSS or SIPSv.5.6-DSM-5-APS), sample size, mean age and percent of females, quality assessment (see below) and key findings.

Quality assessment

Study quality was assessed using a modified version of the Newcastle-Ottawa Scale (NOS) for cross-sectional and cohort studies[22,23] (eTable 4).

Systematic review

To systematically assess the validity of DSM-5-APS, the available evidence was structured in 3 main classes of potential validators adapted from Kendler et al[24]:

1. antecedent validators (demographic factors, predisposing and precipitating risk factors);
2. concurrent validators (diagnostic factors and diagnostic agreement, comorbidity, neurobiological and neurocognitive factors, symptom measures and functioning, baseline treatments);
3. prognostic validators (overall prognostic accuracy, risk of psychosis onset, predictors of outcomes, response to treatments).

Meta-analysis

A quantitative meta-analysis was conducted to test the risk of psychosis onset in DSM-5-APS or APSS or SIPSv5.6-DSM-5-APS (Table 1). The risk of psychosis onset was estimated as the proportion of individuals at-risk who developed psychotic disorders (psychosis onset was defined by the SIPS or ICD/DSM) at 6, 12, 24, 36 (or more) months of follow-up, updating a previous publication[25]. A secondary meta-analysis was conducted to address the proportion DSM-5-APS, APSS or SIPSv.5.6-DSM-5-APS individuals presenting with (DSM/ICD) comorbid mental disorders. For these meta-analyses, additional inclusion criterion were non-overlapping samples and availability of at least 3 independent studies reporting on the same outcome. For pooling proportions in a meta-analysis of multiple studies metaprop package 21[26] of Stata statistical software (StataCorp, version 14) was used. The 95% CIs were based on score procedures[25,27]. Since high heterogeneity was expected, random-effects meta-analyses were conducted[28]. Publication biases were assessed with the metafunnel [29] and with the Egger test[30] in metabias[31] functions of Stata; the trim and fill method was used to correct the estimates in the case of publication biases[32]**.** Heterogeneity among study point estimates was assessed using Q statistics. The proportion of the total variability in the effect size estimates was evaluated with the I^2 index[33]. Meta-regressions were planned when there was substantial heterogeneity (>50%) and at least 10 studies per each outcome.

RESULTS

Database

The literature search yielded 27852 citations, which were screened for eligibility; 56 articles reporting on 124 validators were included in the systematic review (Figure 1): 15 antecedent validators, 55 concurrent validators and 54 prognostic validators. 21 and 10 of the 56 studies were used for the risk of psychosis and comorbid mental disorders meta-

analyses, respectively. 46 studies employed the APSS designation, 5 the DSM-5-APS, 5 both APSS and DSM-5-APS (in 1 study[17] the sample was mixed and in 4 studies[16,24,25,26] the sample met both criteria) and none acknowledge using the SIPSv5.6-APS-DSM5. The total sample size of the studies included ranged from 21[34] to 2101[35] individuals; the DSM-5-APS/APSS sample size ranged from 4[36] to 689[37] and the age of participants ranged from 14.6[38] to 24.8[14]. There were 26 studies from the US, 16 from Europe, 11 from Australasia and 3 across different countries.

Antecedent validators

Demographic factors

The epidemiological prevalence of the DSM-5-APS in the general non-help seeking young population is 0.3%[36] (eTable 5a). The onset/worsening criterion C excluded 2.3% of the general population who felt distressed by attenuated psychotic symptoms[36]. The prevalence of the APSS is 1.3%[39] in the general population and 3.5% in college students[40]. The prevalence of APSS in clinical samples was highly variable ranging from 3.1%[35] to 80%[41]; the effect of age on the prevalence of DSM-5-APS/APSS in help-seeking samples was inconsistent[38,41,42].

Retrospectively, 44% of patients diagnosed with schizophrenia would have met DSM-5-APS criteria in the past[15].

Predisposing and precipitating risk factors

47.8% of APSS individuals reported having experienced at least one type of trauma (eTable 5b)[43]. Younger APSS individuals (15-18 years) have better social and role functioning scores, less depressive symptoms than the older individuals[38]. Social dysfunction in APSS is associated with symptoms distress[8].

Concurrent validators

Diagnostic factors and diagnostic agreement

Assessors agree with the gold standard on the presence or absence of DSM-5-APS 70% (kappa= 0.34), of the times[44] (eTable 6a). Pre-screening tools have robust psychometric properties for recognising APSS[45]. The inter-rater reliability for DSM-5-APS (kappa= 0.46) is comparable to that of other DSM-5 mental disorders[10]. As noted in the introduction, the diagnostic agreement between the DSM-5-APS and the CAARMS 12/2006 is only moderate (kappa= 0.59)[14].

Comorbidity

Despite criterion E, about half (49%) of DSM-5-APS/APSS individuals presented with comorbid depressive disorders, 22% with bipolar disorder, 38% with anxiety disorders, 9% with generalised anxiety disorder, 13% with obsessive-compulsive disorder, 20% with substance use disorders, 13% with cannabis abuse, 7% with alcohol abuse and 22% with social phobia (meta-analytical results are reported in eTable 7-8). Other comorbid disorders that were not meta-analysed because there were less than 3 studies included attention deficit hyperactivity disorder[46,47], oppositional defiant disorders[17], conduct disorders[17,38] and posttraumatic stress disorder (eTable 6b)[42]. Personality disorder traits were also frequent (57.1%)[17], in particular schizotypal personality disorders (rates varied between 17.0%[38] and 67.8%[18]) and borderline personality traits (42.9%[17]). Lifetime suicidality was more frequent in DSM-5-APS/APSS than non-DSM-5-APS/APSS help-seeking individuals[41,42]: about 26.3%[48]-38.9%[17] of the DSM-5-APS/APSS population suffered at least one lifetime suicide attempt and suicidal ideation reached 77.8%[17]. The APSS designation was also associated with an increased risk of violence[49].

Neurobiological and neurocognitive factors

Neurocognition[47,50] (particularly vigilance and processing speed[51]), social cognition[50] and

metacognition[47] (which related to self-disturbances[46]) were impaired in APSS subjects compared to controls (eTable 6c). Olfactory deficits in APSS individuals were associated with the severity of negative symptoms[34]. APSS individuals displayed enhanced fronto-temporal functional brain connectivity[52] and reduced mismatch negativity compared to controls[53].

Symptom measures and functioning

Compared to other help-seeking samples, DSM-5-APS/APSS individuals were more severely ill[17,41], depressed[17], distressed[35] and with a poorer functioning[17,41] (eTable 6d). The severity of attenuated psychotic (positive, negative, disorganised and general) symptoms was significantly higher in APSS than non-APSS help-seeking individuals[41,42]; attenuated psychotic symptoms were also associated with obsessive-compulsive traits, interpersonal sensitivity and depression[40]. The most frequent unusual thought contents were being perplexed by reality and having overvalued beliefs[54]. The most frequent perceptual abnormalities were simple auditory[43,54] (typically hearing their own voice with a negative content[54]) or simple visual[43]; tactile, olfactory or complex perceptual abnormalities were more infrequent. The severity of perceptual abnormalities was also lower in males compared to females[43] and in those with simple compared to complex perceptual abnormalities[43]. The presence of violence content in attenuated psychotic symptoms was associated with increased anxiety, negative beliefs towards self and others and bullying[55].

Baseline treatments

Baseline treatment exposure was: 5.5% - 57.1 % for antipsychotic medication[16-18,53,56-62] (mostly atypicals[53,56]), 0.0%-38.1 for antidepressants[16-18,58-63] and 4.0%-20.8% for a combination of both[16,18,41,60-62,64]; 4.3%-33.3% for mood stabilisers[17,58], 9.8%-14.3% for anxiolytics[17,58], and 4.3% for other psychotropic drugs (methylphenidate, antiepileptics)[41] (eTable 6e).

Prognostic validators

Overall prognostic accuracy

There was only one study reporting on DSM-5-APS prognostic accuracy which resulted acceptable (AUC=0.76) at 24 months and comparable to that of the CAARMS[14]; those meeting DSM-5-APS criteria had a 5-fold probability of transitioning to psychosis compared to those high-risk individuals not meeting DSM-5-APS criteria (eTable 9)[14].

Risk of psychosis onset

23 independent studies (1 in DSM-5-APS and 22 in APSS) reported risk of psychosis onset at follow-up, with an overall sample size of up to 2376 participants. The meta-analytical psychosis risk was 11% at six months, 15% at 12 months, 20% at 24 months and 23% at 36 months follow-up (Figure 2, Table 2 and eTables 10-13). There were publication biases at 12-month and 24-month that were corrected with the trim and fill method (Table 3 and eTables 14-17). Meta-regressions did not show any effect of age, gender, publication year and study quality (eTable 18). In the only study employing DSM-5-APS, there was a 28% risk of psychosis at 21-month[14].

Predictors of outcomes

Mean age at the time of psychosis onset was 20.3 years for males and 23.5 years for females[16], with a transition time of 234 days[65] (eTable 9b). Of those who developed psychosis, 64.8% received a diagnosis of DSM schizophrenia[61]. 85.1% of individuals reached psychotic intensity on unusual thought content, 43.3% on suspicious ideas, 13.4% on grandiose ideas and 46.3% on perceptual abnormalities[65]. Psychosis onset was characterised by the presence of Asian or Pacific Islander race[16], and the emergence of new symptoms[65] along with more severe and persisting positive/negative/general[16,18,61] symptoms, and lower subjective well-being[56,66].

Attenuated odd ideas[16], thought disorder[16], unusual thought content[59,61] and auditory perceptual abnormalities[60] were associated with a higher risk for psychosis, while visual perceptual abnormalities with a lower risk[60]. Speech features[64], in particular disorganized communication[58,59] were also associated with an increased risk of psychosis, as well as a decline in social functioning[58,59]. Verbal memory deficits[51,59,58], verbal fluency[59], processing speed[51,59] and composite cognitive measures[51] were associated with an increased risk of psychosis. Similarly, abnormalities in emotional processing[45,67], motor dysfunction[62], olfactory dysfunction[34] and mismatch negativity[53] were associated with an increased risk of psychosis. Schizotypal personality disorder was not associated with increased risk of psychosis[18] but axis II disorders along with familial psychiatric history, tobacco use, number of hospitalisations, history of trauma were associated with suicide attempts[48]. None of these predictors was externally replicated.

Response to treatment

Naturalistic studies found that 25.5% of individuals received antidepressants for an average of 3-month with no improvement in negative symptoms or social functioning[63] and that 48% of individuals showed little improvement in their symptoms, after one year, despite being treated with supportive therapy and/or psychotropic medication[56] (eTable 9d). The only available randomised controlled trial found no significant differences in risk of psychosis onset, improvement of severity of symptoms or functioning between cognitive behavioural therapy and supportive therapy[68].

Quality assessment

The NOS scores ranged from 3 to 8 (eTables 19-20).

DISCUSSION

While there are many meta-analyses on CHR-P in the literature, to our knowledge, this is the first systematic review that specifically addressed the clinical validity of DSM-5 APS across 56 studies and 124 validators. Most of the evidence reviewed focused on concurrent and prognostic validators in APSS individuals, while antecedent factors were rarely investigated.

The systematic review of antecedent validators identified only a few records. The prevalence of DSM-5-APS is 0.3% in the general population[36], 3.5% in college students[40] and highly variable in clinical samples[14,41,42]. The latter point reflects the significant sampling biases that affect the CHR-P/APSS paradigm[69-73]. There is an overall paucity of robust epidemiological research addressing the specific risk or protective factors that may exert a predisposing or precipitating role in the DSM-5-APS/APSS. While recent reviews have indicated that psychosis onset is largely driven by non-purely genetic risk factors[74,75 22], it is not clear how these factors accumulate in DSM-5-APS/APSS samples. A further public health limitation is that only half of individuals would report a DSM-5-APS like state preceding their first episode of schizophrenia[15], questioning the universality of this syndrome as pre-psychotic stage. Other retrospective cohort studies have confirmed a reasonably large subgroup (30%) of first episode of psychosis patients for whom there is no evidence of meeting prior CHR-P criteria for any identifiable length of time[76,77]. The possibility that non-psychotic risk syndromes could precede the first onset of psychosis was recently summarised at meta-analytical level[78].

The systematic review identified more concurrent validators. Inter-rater reliability for DSM-5-APS is comparable to that of other DSM-5 mental disorders, although the confidence intervals of the field test were very large[10]. Noticeably, the reliability of the DSM-5-APS can be optimised if the SIPSv5.6 is being used. Unfortunately, to date, only a few studies have acknowledged using this specific SIPS version. Furthermore, despite the criterion E requiring a differential diagnosis, half of the individuals meeting DSM-5-

APS/APSS had comorbid major depressive disorders (table 2). This is in line with phenomenological accounts highlighting the role of mood dysregulation during the phases that precede the psychosis onset[79] and supporting the notion that psychosis may arise from multiple psychopathological spectra[80]. Given that psychosis onset can occur from non-psychotic risk syndromes, the removal of this criterion may improve both its prognostic performance and transdiagnostic value[11,14,81]. Symptomatically, the DSM-5-APS/APSS individuals were more severely ill, more depressed and with a poorer functioning than other help-seeking samples not meeting the DSM-5-APS/APSS, with a duration of untreated attenuated psychotic symptoms was around 710 days[25]. Attenuated positive psychotic symptoms more frequently included derealisation, overvalued beliefs and simple auditory abnormalities[43,54] and the presence of violence content was associated with high distress[55]. This supports the notion that DSM-5-APS indexes a clinical syndrome which is disabling per se and independent from the outcomes[23,81]. In fact, the vast majority of DSM-5-APS/APSS individuals had suicidal ideation and up to one-third of them attempted suicide[17]. At baseline, up to 57% of individuals received antipsychotic medication[17], 38% antidepressants[17] and 33% mood stabilisers[17], corroborating the polymorbid distressing nature of this syndrome. Neurocognitive[47,50,51], social cognitive[50] and metacognitive[47] dysfunction, although not diagnostically required, are also frequent, while neurobiological research into DSM-5-APS/APSS is too limited to draw reliable conclusions.

The systematic review of prognostic validators confirmed that DSM-5 APS prognostic accuracy is acceptable (AUC=0.76) at 24 months and comparable to the CAARMS[14]. Individuals meeting DSM-5 APS/APSS criteria had a 5-fold probability of transitioning to psychosis compared to those high-risk individuals not meeting these criteria, with a 23% risk of psychosis at 36 months follow-up (Figure 2, Table 2 and eTable 13). The only study employing DSM-5-APS criteria reported a 28% risk of psychosis onset at 21-month[14]. Of those who converted, around 2/3 received a diagnosis of schizophrenia[61].

These findings indicate a substantial risk of progression to psychosis, on top of the baseline distressing clinical profile of the syndrome. However, predicting clinical outcomes in this population is currently hampered by the lack of externally validated prognostic models[82]; available models developed with stepwise approaches[58] did not replicate well in external samples[59]. There was very limited evidence relating to effective treatments for DSM-5-APS/APSS, in line with the current state of knowledge of the CHR-P field[83]. Only one randomised controlled trial compared cognitive behavioural therapy and supportive therapy without finding differences between them[68]. Some trials are ongoing and are addressing the potential effects of treatments on clinical remission and functional outcomes[81] beyond psychosis onset[84].

The potential clinical validity of DSM-5-APS is further confirmed by surveys conducted in the general public and health care professionals (eTable 21). Most practitioners consider DSM-5-APS to constitute a mental disorder[98] in which medication, family involvement and cognitive coping skills can be helpful[99]. Importantly, in none of these surveys involving the general public, health care professionals[100], undergraduates[101] and college students[102], the levels of stigma associated with the DSM-5-APS /APSS were perceived higher than other mental disorders or than other psychotic-like experiences[100,101].

The main limitation of this review is the scarce amount of evidence on precipitating and predisposing factors, neurobiology and preventive treatments. A further important limitation is that the vast majority of studies employed the APSS designation which does not exactly match the DSM-5-APS. For example, some studies measured APSS and considered them as DSM-5-APS without clarifying the SIPS version used[17,34,37-43,45-47,49,51-60,62-64,66-68,85-96] or whether the symptoms were distressing and disabling to the patient to warrant clinical attention[42,97]. Therefore, this review supports the clinical utility of the APSS and since the DSM-5 APS is most similar, it is supporting the DSM-5 APS

clinical utility. Future studies are required to carefully avoid confusing CHR-P operationalisations with the DSM-5-APS category, by testing all the criteria A to F (Table 1) upfront, either clinically or using the SIPSv.5.6-DSM-5-APS (Table 3). Accordingly, the text describing the DSM-5-APS should be revised for accuracy and consistency with the specific evidence presented here. Most importantly, the revision of the DSM-5-APS should carefully overcome the current misleading availability of different specifications across the main text and research appendix (eTable 1). Because of such inconsistency, individuals at risk of psychosis may be mislabelled under the rubric of "Other Specified Schizophrenia Spectrum and Other Psychotic Disorder"[42]. Furthermore, with few exceptions[43,54,55], most studies were carried out in relatively small samples.

CONCLUSIONS

Current evidence supports the potential clinical validity of the DSM-5-APS. However, more research is required to clarify the epidemiological profile of this diagnosis, its predisposing and precipitating risk factors, neurobiological correlates and to identify effective treatments.

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Table 1. DSM-5-APS Attenuated Psychosis Syndrome diagnostic criteria compared with SIPS and CAARMS operationalisations.

	DSM-5-APS (2013)[1]	**APSS SIPS** (from 1998 onwards)[4-6]	**SIPSv.5.6-DSM-5-APS** (2014)	**CAARMS APS** (12/2006)[7]
Diagnostic criteria				
Severity	A. At least one of the following symptoms is present in attenuated form, with relatively intact reality testing, and is of sufficient severity or frequency to warrant clinical attention: 1. Delusions 2. Hallucinations 3. Disorganised speech	SOPS-positive symptom scales P1. unusual thought content, P2. suspiciousness, P3. grandiose ideas, P4. perceptual abnormalities, P5. disorganised communication, with at least one of these symptoms rated 3, 4, or 5 indicating clinically significant disturbance below a psychotic level of intensity	As for APSS	CARMS-positive symptoms scales rated 3-5 (P1. unusual thought content, P2. non-bizarre ideas), 3-4 (P3. perceptual abnormalities), 4-5 (P4. disorganised speech)
Frequency	B. Symptom(s) must have been present at least once per week for the past month	Symptoms ever been present at an average frequency of at least once/week over a month	As for APSS	Symptoms present from 1/month to 2/week, >1 h per occasion, OR 3 to 6/week, <1 h per occasion
New onset and worsening	C. Symptom(s) must have begun or worsened in the past year	Begin within the past year, or any currently rate one or more scale points higher compared to 12 months ago; rated only symptoms that occurred over the past month	As for APSS	Need to be present in the past 12 months; rated the most severe in the past 12 months
Distress/disability	D. Symptom(s) is sufficiently distressing and disabling to the individual to warrant clinical attention	Subjective qualifier not used to assign the designation	Attenuated positive symptoms sufficiently distressing and disabling to the patient to warrant clinical attention	Rated on a scale 0-100 but not used to assign the designation
Differential diagnosis	E. Symptom(s) is not better explained by another mental disorder, including a depressive or bipolar disorder with psychotic features, and is not attributable to the physiological effects of a substance or another medical condition	Symptoms ever not been explained better by another DSM disorder	As for APSS	No requirement for differential diagnosis with other mental disorders

Lack of lifetime psychotic disorder	F. Criteria for any psychotic disorder have never been met	Severity score of 6 on at least one of P1–P5 AND symptoms ever occur for at least 1h/day at an average frequency of four days/week over one month OR symptoms are seriously disorganising and dangerous (urgency criteria)	As for APSS	Severity score of 6 on at least one of P1, P2, P4 and/or 5–6 on P3 AND frequency of at least 3 to 6/week, > 1 h per occasion, or daily, <1 h per occasion AND symptoms present for longer than one week. Urgency criteria not considered.
Substance misuse	Assessed within criterion E	Exclude if symptoms are strongly intertwined temporally with substance use episodes	As for APSS	Exclude if symptoms occur only during peak intoxication from hallucinogens, amphetamines and cocaine; included if due to cannabis or alcohol
Antipsychotic treatments	Not assessed	Usually assessed and considered as an exclusion criterion	As for APSS	Usually assessed and considered as an exclusion criterion
Functional decline	No social/occupational dysfunction decline requirement	No social/occupational dysfunction decline requirement	As for APSS	30% drop in SOFAS score from premorbid level, sustained for a month, within the past 12mo OR SOFAS score <50 for the past 12 months or more
Assessment	Unstructured clinical interview	Semi-structured psychometric interview	As for APSS	Semi-structured psychometric interview
Duration of the assessment	From 20'[14] to 45'[44]	About 2 hours	As for APSS	About 2 hours
Specific psychometric training	Not required	Required	As for APSS	Required

*SOFAS: Social and Occupational Functioning Assessment Scale.

Figure 1. PRISMA flowchart outlining study selection process

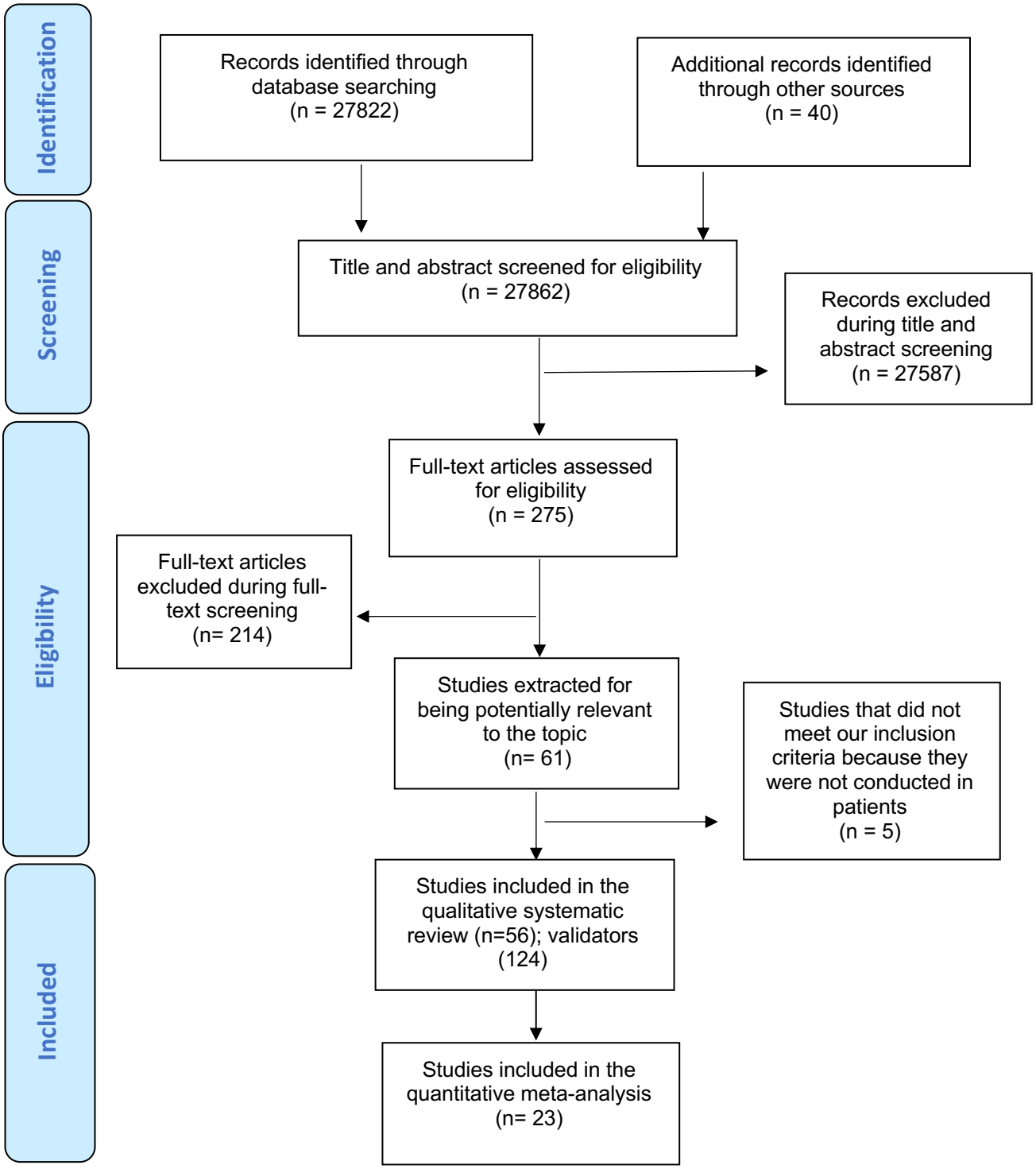

Figure 2. Cumulative risk of psychosis onset in DSM-5-APS/APSS

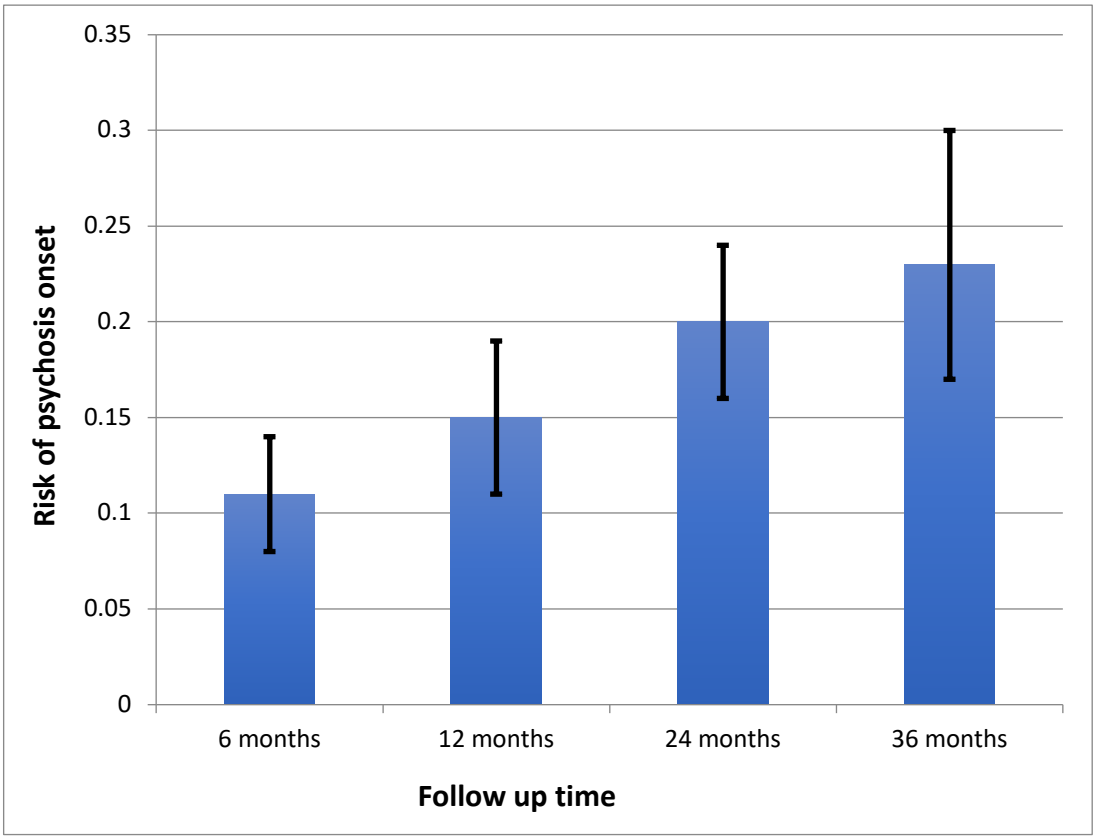

Table 2 to Figure 2. Cumulative risk of psychosis onset in individuals with DSM 5-APS/APSS

Follow-up	n of studies*	Total DSM-5-APS/APSS sample	Cumulative risk of psychosis	95%CI	Q	df	I2	P
6-month	12	824	0.11	0.08-0.14	20.77	11	47.04	0.04
12-month	19	1292	0.15[(a)]	0.11-0.19	61.02	18	72.14	<0.01
24-month	18	2212	0.2[(b)]	0.16-0.24	87.22	17	79.36	<0.01
36-month	7	721	0.23	0.17-0.30	22.2	6	72.97	<0.01

* all studies but one[14] refer to APSS; a) 0.104, 95%CI 0.062-0.145 after the fill and trim method; b) 0.139, 95%CI 0.097-0.182 after the fill and trim method.

Table 3. Evidence-based reporting recommendations for future DSM-5-APS clinical research

1	Test the specific DSM-5-APS criteria A to F upfront in a standard psychiatric clinical assessment
2	Report the exact number of patients meeting the specific DSM-5-APS criteria A to F
3	If CHR-P instruments are being used indicate their type and version and stratify the findings across APSS/APS, GRD and BLIPS/BIPS subgroups
4	Preferably use the SIPSv.5.6 for the psychometric assessment of DSM-5-APS; ensure an appropriate training
5	If both clinical DSM-5-APS and psychometric APSS/APS criteria are tested in the same patients, detail their concordance/discordance.

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